REMARKS

Applicants believe no new matter is added by this amendment. This amendment is being made in response to the Office action and was not made previously for that reason.

Amendments to the claims.

Claims 1-61 were canceled in previous amendments. Claims 62-69 and 75-77 are currently amended. After entry of the instant amendment, claims 62-77 will remain pending. Applicants believe that present amendments place this application in better condition for appeal or allowance.

Support for the amendments to the claims may be found, for example, with the following disclosures:

For "more toleran[ce] to salt or osmotic stress" resulting from overexpression of a claimed sequence in "transgenic seedling[s] or more mature plant[s]", a basis may be found, for example:

on page 93, on lines 25-32 of the instant application ("For stress experiments conducted with more mature plants, seeds were germinated and grown for seven days …"), and on page 101, lines 8-9 ("Plants overexpressing G482 orthologs may also be subjected to soil-based drought assays to identify those lines that are more tolerant to water deprivation than wild-type control plants"; soil based assays are conducted with more mature plants, as evidenced on page 87, lines 10-11: "168 hours after removing water from trays"), and on page 9, line 31 ("after eight days"), page 10, lines 21-23 ("44 days after germination" and "24 days after germination"), and line 28 ("post-germination");

on page 86, lines 15-16 ("Evaluation of germination and seedling vigor was conducted 3 to 15 days after planting. The basal media was 80% Murashige-Skoog medium (MS) + vitamins. For salt and osmotic stress experiments, the medium was supplemented with 150 mM NaCl or 300 mM mannitol.");

on page 92, lines 8-10 ("35S::G485 lines showed enhanced cotyledon expansion and root growth seen in the overexpressing seedlings in cold, high sucrose, high salt and ABA treatments, as compared to wild-type controls");

on page 89, lines 14-16 ("35S::G481 plants were also significantly larger and greener in a soil-based drought assay than wild-type controls plants. After eight days of drought treatment overexpressing lines had a darker green and less withered appearance … than those in the control group");

on page 93, lines 13-15 ("One of the lines of G3395 overexpressors tested was found to be more tolerant to high salt levels, producing larger and greener seedlings in a high salt germination assay"); and

Support for "more toleran[ce] to salt or osmotic stress" in "transgenic seedling[s] or more mature plant[s]" is also found, for example:

in priority application 09/713,994, filed 11/16/2000, on page 8, lines 17-19 ("Plant growth characteristics that can be modified include growth rate, germination rate of seeds, vigor of plants and seedlings");

on the CD-ROM provided as "Appendix A", filed with priority application 09/713,994 on 11-16-2000 on the page "Summary of Overexpressor G482, Family CAAT" ("G482 overexpressors are more tolerant to high NaCl in a germination assay. Further experiments should be done to determine the utility of this degree of NaCl tolerance under field conditions"; a courtesy copy of this page is provided); and

on the page "Physiology of Overexpressor G482, Family CAAT" ("Plants overexpressing G482 show slightly increased seedling growth when germinated on high salt"; a courtesy copy of this page is provided).

Support for "more toleran[ce] to salt or osmotic stress" in "transgenic seedling[s] or more mature plant[s]" is also found, for example:

in priority application 60/166,228, filed 11/17/1999, on page 6, lines 10-11 ("Plant growth characteristics that may be modified include growth rate, germination rate of seeds, vigor of plants and seedlings"), and on the pages "Summary of Overexpressor G482, Family CAAT" and "Physiology of Overexpressor G482, Family CAAT". Please note that the latter two pages are nearly identical to the Summary and Physiology descriptions on the attached copies of the pages from Appendix A of priority application 09/713,994.

Additional support for the amended claims can be determined from the response to Item 3 of the latest Office action, provided below.

Response to specific items in the Office action

Item 3. Priority

The Office action states that "claims 62-77 are given the priority date of 30 September, 2003, the instant application" (Office action, page 3).

Applicants note that the instant claims are directed to plants that overexpress the G482 sequence and are more tolerant to salt OR osmotic stress, and respectfully submit that the Patent Office may have overlooked disclosures in Applicants' priority documents which support the presently claimed invention.

The instant application claims U.S. patent application 09/713,994, filed 11/16/2000, as a priority application. U.S. patent application 09/713,994 discloses the G482 DNA as SEQ ID NO: 25 of that application. SEQ ID NO: 25 encodes the complete G482 polypeptide. See also Figure 1 of U.S. patent application 09/713,994, which discloses "[SEQ ID No.] 25…[GID] G482…[conserved domain in amino acid coordinates] 25-116". See also Figure 2: "[SEQ ID No.] 25…[GID] G482…[Overexpressor (OE) or knockout (KO)] OE…[phenotypic observations] increased tolerance to high salt". The application also states

that "Plant growth characteristics that can be modified include growth rate, *germination rate of seeds*, *vigor of plants and seedlings*" (page 8, lines 17-19), "Plants were exposed to chilling stress … high salt stress (6 hour exposure to 200 mM NaCl), drought stress (168 hours after removing water from trays), osmotic stress (6 hour exposure to 3 M mannitol)" (page 40, lines 3-6), "wash conditions of 0.2x SSC to 2.0 x SSC, 0.1% SDS at 50-65^{o} C, for example *0.2 x SSC, 0.1% SDS at 65° C*" (page 12, lines 8-9), or page 11, lines 13-15: "Factors that are most closely related to the listed sequences share, e.g., *at least about 85%*, about 90% or about 95% or more % sequence identity to the listed sequences" (*emphases* added).

U.S. patent application 09/713,994 claims US provisional application 60/166,228 as a priority application. US provisional application 60/166,228 discloses the G482 sequence and associated trait on page 352-354 of the 781 page "Miscellaneous Incoming Letter" available on PAIR; "G482 overexpressors are more tolerant to NaCl in a germination assay… Further experiments should be done to determine the utility of this degree of NaCl tolerance under field conditions." On page 353, the complete G482 polypeptide sequence is provided. On page 11 beginning at line 15 of the specification is found the disclosure for "Nucleic acid molecules that hybridize under stringent conditions will typically hybridize to a probe based on either the entire cDNA or selected portions of the cDNA under wash conditions of 0.2x SSC to 2.0 x SSC, 0.1% SDS at 50-65^{o} C, for example *0.2 x SSC, 0.1% SDS at 65° C*". On page 10 beginning at line 32 is found: "Factors that are most closely related to the disclosed sequences share *at least 85%*, 90% or 95% sequence identity." (*emphases* added).

The instant application claims priority from US patent application 10/286,264, filed 11/01/2002, which is a division of US patent application 09/533,030, filed 03/22/2000, both of which have similar disclosures as discussed above, e.g., page 24, lines 1-4 of application 09/533,030: "Plants containing the G482 construct [SEQ ID NOs: 13, 14] showed a higher germination rate and more vigorous seedling growth than controls with 150 mM sodium chloride, so G482 could be used for conferring salt tolerance to germinating seedlings", page 12, line 13: "0.2 x SSC, 0.1% SDS at 65° C"; and page 11, lines 30-32: "Factors that are most closely related to the disclosed sequences share *at least 85%*, 90% or 95% sequence identity" (*emphasis* added).

The latter two applications claim priority to US provisional patent application 60/125,814, filed 03-23-1999. This provisional application discloses all but the first few amino acids of the G482 sequence, which may be found on page 717 of the 1095 page "Miscellaneous Incoming Letter" available on PAIR (this is the same publicly available sequence that was available to Edwards for the publication noted below). "Transcription factors that are most closely related to the disclosed nucleotide sequences share *at least 85%*, 90% or 95% sequence identity with one or more of the disclosed Arabidopsis transcription factor proteins" is found on page 50 (page 48 of the specification) on lines 2-5". "Nucleic acid molecules that hybridize under stringent conditions will typically hybridize to a probe based on either the entire cDNA or selected portions

of the cDNA under wash conditions *of 0.2x SSC, 0.1% SDS at 65°C*" beginning on line 17 of page 48 (specification page 46) of the "Miscellaneous Incoming Letter". This application also discloses that "Desirable changes in a seed's phenotype *include its germination characteristics*; shelf-life; drydown characteristics; size; stress responses, such as to heat, cold, *salt or osmotic shock*" (*emphasis* added; in lines 32-34 of page 3 of the "Miscellaneous Incoming Letter", page 1 of the specification). The application also discloses that "Transgenic seed are tested for different germination phenotypes, for example, whether seeds *germinate* under heat or cold stress or under conditions of poor soil quality such as conditions of *salt stress or osmotic stress*" (lines 7-10, page 67 of the "Miscellaneous Incoming Letter", page 65 of the specification) and "For *salt and osmotic stress* experiments, the LD50 for wild-type seeds were determined to be 150 mM NaCl and 300 mM mannitol respectively. Seeds, either wild type or transgenic, are *germinated* in 150 mM NaCl, or 300 mM mannitol" (*emphases* added).

Accordingly, Applicants believe the instant and priority applications 10/286,264, filed 11/01/2002, 09/533,030, filed 03/22/2000, 09/713,994, filed 11/16/2000, 60/166,228, filed 11/17/1999, and 60/125,814, filed 03/23/99, disclose the present sequences, seedlings or more mature transgenic plants, hybridization conditions of 0.2x SSC, 0.1% SDS at 65°C, at least 85% amino acid identity, and methods for determining salt stress or osmotic stress tolerance.

Item 6. 35 U.S.C. §112, first paragraph, enablement

Claims 62-77 stand rejected under 35 U.S.C.§ 112, first paragraph, on the basis that the specification, while being enabling for a method of making and a transgenic plant made, comprising a recombinant polynucleotide encoding a polypeptide of SEQ ID NO: 4 that exhibits increased germination when grown on high salt or mannitol-containing medium and increased heat tolerance, does not reasonably provide enablement for methods of making and transgenic plants made comprising other recombinant polynucleotides. The rejection under 35 U.S.C. §112, first paragraph, is respectfully traversed with the following remarks.

The Examiner reasons that the Specification does not adequately enable the skilled artisan "to determine "which of the other asserted species would meet the limitations of the instant claims, i.e., by hybridizing to SEQ ID NO: 3". The Patent Office further cites Applicants' arguments presented in response to the 35 U.S.C. §103 rejection in support of it's proposition that "whether a plant transcription factor, when overexpressed in a plant, will give a specific phenotype is highly unpredictable".

With respect to whether other asserted species would meet the limitation of the instant claims, Applicants note that the specification discloses four different polypeptide sequences (G482, G481, G485, and G3395, SEQ ID NOs: 2, 4, 6 and 74, respectively) from diverse dicot and monocot plant species that, when overexpressed in plants, confer increased salt and/or osmotic stress tolerance (e.g., Table 6).

Applicants note that they have also taught structural features that would be recognized by one of skill in the art at the time of the invention to identify sequences orthologous to G482. For example, amino acid residues 26-116 of G482 make up a to CCAAT-box binding conserved "B domain" that is recognizable by specific amino acids indicated by Applicants, and distinguish the sequences of the claimed invention from other known CCAAT-box binding transcription factors such as LEC1. See, for example Figure 3 the non-LEC1-like clade claimed sequences are distinguished from the LEC1 clade, the alignment in Figure 6B-6C and the description in the specification on page 29, line 18 through page 30, line 4.

Furthermore, Applicants bring the Examiner's attention to the attached Exhibit A which aligns the nucleotide encoding sequences of the B-domains of four G482 related species which Applicants have shown in the application to confer the claimed traits upon expression in transgenic plants, and draw the Examiner's attention to the high degree of similarity between these DNA sequences, particularly notable in the pair-wise alignments.

Applicants note that the independent claims have also been amended to recite a specific function for the claimed sequences and the specification teaches assays for determining these functions, as noted above. The Examiner has provided no reason or evidence to support the position that the ordinary artisan could not identify whether a protein had salt and/or osmotic stress conferring tolerance imparting function and therefore has failed to establish a reasonable basis to question the enablement.

With respect to the Patent Office's position in this rejection related to unpredictability, Applicants note that the Swindell and Feder references cited previously by Applicants are directed to analysis of genes based solely on transcription response or relative abundance in various plant tissues. In contrast, the present application provides the experimental and functional analysis lacking in those references, and demonstrates the use of the claimed sequences to produce actual phenotypes in transgenic plants, as well as identifying other species likely to confer the same or similar results based on sequence analysis of functional domains. Thus, the skilled artisan has knowledge of and is well able to follow detailed teachings in the specification describing how to clone, transform, express and evaluate the encoded polypeptides of disclosed DNA sequences, such as those encoding G482 related proteins identified in Table 1, that are likely to encode functional CCAAT-binding transcription factors that confer the same or similar abiotic stress properties upon expression in transgenic plants. Whether every transgenic plant made in an experiment will express a functional transcription factor is not at issue, since not all iterations of the claims must be functional, and since some experimentation is permissible.

Additional teachings in the present application that enable the skilled artisan to practice the instant invention include the following:

The Specification teaches how to identify putatively orthologous sequences using sequence identity and hybridization methods (e.g., beginning on page 43, line 23).

The specification describes how to transform various diverse plants (e.g., Examples XIII and XIV).

The Specification describes specific assays to identify functional polypeptides that confer increased salt and/or osmotic stress tolerance when the polypeptides are overexpressed in plants (e.g., beginning on page 87, line 24).

Applicants note that the Examiner has made no factual findings regarding the quantity of experimentation necessary to carry out the invention.

"The essential question here is whether the scope of enablement ... is as broad as the scope of the claim[s]." *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991). Applicants believe that the Examiner has not provided sufficient evidence to show that it would have required undue experimentation to practice of the full scope of the claimed invention.

Other than breadth of the claims, the other Wands factors favor Applicants, particularly "the amount of direction or guidance presented", "the state of the prior art", and "the relative skill of those in the art," *In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988).

The "predictability or unpredictability of the art" also weighs in favor of Applicants, since the use of hybridization methods is routine as shown by Kashima et al. 1985. *Nature* 313:402-404, and Sambrook et al. 1989. Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.; and by Haymes et al., Nucleic Acid Hybridization: A Practical Approach, IRL Press, Washington, D.C. 1985, which references were incorporated by reference. Sequence identity comparison is also routine, as evidenced by Hein 1990. *Methods Enzymol.* 183: 626-645, who teach methods for determining percentage identity. Furthermore, methods for finding similar sequences are taught by Bairoch et al. 1997. *Nucleic Acids Res.* 25: 217-221; Smith et al. 1992. *Protein Engineering* 5: 35-51; Altschul 1993. *J. Mol. Evol.* 36: 290-300; Altschul et al. 1990. *J. Mol. Biol.* 215: 403-410; Henikoff and Henikoff 1991. *Nucleic Acids Res.* 19: 6565-6572; Eddy 1996. *Curr. Opin. Str. Biol.* 6: 361-365; Sonnhammer et al. 1997. *Proteins* 28: 405-420, and the like. Databases, algorithms and other methods are well known in the art and are described in Ausubel et al. 1997. Short Protocols in Molecular Biology, John Wiley & Sons, New York, NY, unit 7.7; and Meyers 1995. Molecular Biology and Biotechnology, Wiley VCH, New York, NY, p 856-85, and are available on-line, for example, at the National Center for Biotechnology Information (e.g., at blast.ncbi.nlm.nih.gov/Blast.cgi).

Furthermore, the skilled artisan understands how to transform plants (e.g., see Moloney et al. 1989. *Plant Cell Reports* 8: 238; Vasil 1994. *Plant Mol. Biol.* 25: 925-937; Nandi et al. 2000. *Curr. Biol.* 10: 215-218; Weigel and Nilsson 1995. *Nature* 377: 482-500; Weissbach and Weissbach 1989. Methods for Plant Molecular Biology, Academic Press, and Gelvin et al. 1990. Plant Molecular Biology Manual, Kluwer Academic Publishers; or Peng et al. 1999. *Nature* 400: 256-261) and test transformed plants (e.g.,

Thomashow et al. 2002. US Patent No. 6,417,428; Haake et al. 2002. *Plant Physiol.* 130: 639-648) for the claimed functions, and can also understand and follow the methods provided in the instant application.

It is well settled that Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). There must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill in the art how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the skilled artisan to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclose utility. In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991). In the instant fact pattern, there is significant disclosure of methods for making and identifying transgenic plants that are salt and/or osmotic stress tolerant, and actual reduction to practice with four sequence species.

Applicants believe that the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention and that no such evidence or scientific reasoning is present in the instant rejection. See *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). Applicants believe that, based on the knowledge in the art of how to identify related sequences by hybridization or sequence similarity, coupled with the knowledge of how to make and test transgenic plants, has a success rate much greater than that required by Wands.

Thus, one of skill in the art would thus clearly understand that by this disclosure Applicants have enabled another skilled artisan to practice the claimed plants, and methods of making, made with proteins from a family with an art-recognized correlation between structure and function (e.g., transcriptional regulation, as taught by Edwards and others).

In light of these amendments, and arguments, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement, be withdrawn.

Item 7. 35 U.S.C. §103(a)

Claims 73-104 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Edwards et al ("Edwards"; July 1998, *Plant Physiology* 117: 1015-1022) in view of Harada et al ("Harada"; U.S. Patent 6,235,975 B1, filed 24 June 1998), and in further view of Edwards (16 September 1997, Accession No Y13724). The Patent Office's position is that Edwards 1998 provides a CCAAT-box transcription factor that is nearly identical to Applicants' claimed SEQ 3/SEQ 4, but does not provide a transgenic plant comprising the sequence. Harada is cited by the Examiner to remedy the deficiencies of the primary reference by purportedly providing evidence that transformation of plants with sequences encoding CCAAT-box transcription factors is obvious. Edwards 1997 is cited as evidence that the AHAP3b CCAAT

box binding protein was publicly disclosed in September 1997. The Patent Office further suggests that the phenotypic characteristics discovered and claimed by Applicants would flow naturally from the use of the CAAT-box transcription factor to transform a wild type plant (Office Action mailed 25 February 2009). Applicants believe that the rejection is avoided in part by amendments to the claims, and aspects of the rejection that may not be avoided by the present amendment are respectfully traversed with the following remarks.

Applicants conceived of the claimed transgenic plants prior to the Edwards 1998 publication.

The Office action alleges that "Edwards 1997 is cited as evidence that the AtHAP3b, CCAAT box binding protein as publicly disclosed on 16 September 1997". The Office has previously alleged that "One cannot separate the function of the ATHAP3b transcription factor taught by Edwards from its structure" (Final Office action, 02.25.09).

However, the 1997 publication cited by the Office teaches a protein sequence, not the use of said sequence, much less the polynucleotide encoding the protein, or the expression or the ectopic expression of said sequence in a plant. Applicants are not claiming a sequence, but a transgenic plant.

Regarding Applicants previous assertion that they conceived of the invention prior to the Edwards 1998 publication, the rejection of claims 62-77 is again respectfully traversed for the reasons of record, which arguments will not be reiterated herein, except to note as follows. Applicants did conceive of the present invention prior to the publication of the Edwards reference, and did work diligently to reduce the claimed invention to practice, as previously indicated. Edwards therefore does not serve as a basis for a rejection under 35 U.S.C. §102 or §103. Applicants designed primers for a G482-overexpressing plant at least as early as December 3, 1997, and continued to design primers for this sequence up to and after July 10, 1998, the earliest date the Edward publication may have been available to the public. There is no requirement that the claimed invention must be actually reduced to practice prior to the date of the cited art. Primers were conceived to isolate the G482 sequence. Furthermore, Applicants understood that the G482 sequence, for which the primers were designed, was a transcription factor and therefore had specific and substantial utility. The inclusion of G482 in the CAAT-binding transcription factor family had been ascertained (even an early studies of the partial G482 sequence is listed in the file "12000 annotated ESTs.xls", as a "CAATT-box DNA binding protein subunit B"). The USPTO specifically recognizes that a polynucleotide that encodes a polypeptide with gene-regulating activity has utility, as the USPTO has stated that "[a] claimed DNA may have a specific and substantial utility because, e.g., it hybridizes near a disease-associated gene or it has gene-regulating activity". Utility Examination Guidelines, 66(4) Fed. Reg. 1095 (Jan. 5, 2001).

Harada does not support the Patent Office's position that it was obvious to transform a plant to express a CCAAT-binding transcription factor.

35 U.S.C. §103(a) requires consideration of the "subject matter sought to be patented…as a whole." MPEP §2141. When asserting a *prima facie* case of obviousness, "the burden falls on the [Examiner] to show…that a person of ordinary skill in the art would have had reason to attempt to…carry out the claimed process, and would have had a reasonable expectation of success in doing so. *Pharmastem Therapeutics v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007). Applicants submit that the combination of Harada and Edwards fails in this regard.

Applicants respectfully submit that Harada represents a *significant* teaching away from the instantly claimed invention, particularly in light of the amendments provided herein that specify the transgenic plant of the instant invention is a *seedling or more mature plant*.

There is no discernable useful function associated with LEC1 overexpression in vegetatively growing plants in the Harada patent. Please see column 26, line 7, lines 12-14, and lines 21 to 24 of U.S. patent 6,235,975: [Heading] "*The LEC1 Gene Is Embryo Specific*…we expected the LEC1 gene to have a role mainly during embryogenesis *and not during vegetative growth*…The transcript was detected only in siliques containing young and mature embryos and was not detected in seedlings, roots, leaves, stems and buds indicating that *the LEC1 gene is indeed embryo specific*" (*emphasis* added

Please also see Harada, column 27, lines 61-63: ("[t]he model suggests that LEC1 acts as transcription activator to several sets of genes, which keep the embryonic program on and repress the germination process"). Thus, from the teaching of Harada, the plants that successfully overexpress LEC1 would be unlikely to develop vegetatively. Indeed, the LEC1 overexpression experiments disclosed in Harada (in a Lec1-1 mutant background) demonstrates difficulties associated with such overexpression: "the transformation efficiency was only approximately 0.6% of that obtained normally. In several experiments, half the seeds that germinated (12/23) produced seedlings with an abnormal morphology…Roots often did not extend or extended abnormally and sometimes greened…" (Harada, col. 28, lines 13-19). The majority of plants that did grow vegetatively: "flowered and produced 100% lec1 mutant seeds. Amplification experiments confirmed that the seedlings contained the transgene, suggesting that the 35S/LEC1 gene *was inactive* in these T2 seeds" (Harada, col. 28, lines 29-32, *emphasis* added). Harada thus suggests that the minority of plants that could be grown vegetatively (that is, those that developed into seedlings or more mature plants) could be obtained only when the LEC1 gene was inactive, which is the opposite of the functionality that is required for a sequence that confers traits in seedlings or more mature plants.

Harada also teaches that: "[t]hese seedlings occasionally produced a single pair of organs on the shoot apex at the position normally occupied by leaves. Unlike wild type leaves, these organs did not expand and did not possess trichomes. Morphologically, these leaf-like structures more closely resembled embryonic

cotyledons than leaves." (Harada, col. 28, lines 20-26)". Said plants would be unlikely to provide a motivation to make and use plants that overexpress other CCAAT-binding transcription factors, much less non-LEC1 related sequences.

Thus, the skilled artisan reading Harada would have no expectation that expression of LEC1 or a different CAAT-box binding protein in seedlings or more mature plants, would confer any valuable trait, much less have an expectation of producing plants having tolerance to increased salt or osmotic stress.

Edwards does not alone or in combination with Harada make the presently claimed invention obvious.

Overexpression of a polypeptide in a plant can lead to different results, for example, a plant may be produced that has an advantageous phenotype, a deleterious phenotype (e.g., see above discussion re Harada teaching away from the instant plants and methods), or no discernable alteration of phenotype. Without making the plant, one skilled in the art cannot predict with total accuracy which outcome will occur. Or, in other words, the desired result does not necessarily flow from overexpression of the transgene or polypeptide. The Federal Circuit has ruled that inherent anticipation cannot be "established by probabilities or possibilities, and that, [t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient". *In re Robertson*, 49 USPQ 2d, 1949, 1951 (Fed. Cir. 1999). The court stated that the burden falls on the Examiner to "provide a basis in fact why the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. Inter. 1990) (emphasis in original).

The Examiner has previously stated that because Edwards teaches that "expression of AtHAP3b in leaves from plants grown in soil but not in those from liquid culture may suggest environmental regulation of this gene… perhaps in relation to osmotic stress", the skilled artisan would be motivated to combine the teachings of Harada and Edwards. Applicants note that *environmental regulation* is reactive, a desire for further understanding in developmental and environmental responses in no way implies how overexpression of a sequence will proactively confer function, and thus does not suggest expression studies. Edwards also states that "further research is required to understand the regulation of these factors and their role in developmental and environmental responses"(page 1021, column 1, ¶2). *Responses* are also reactive, and this statement also does not suggest that overexpression of a sequence will proactively confer function.

Furthermore, this teaching by Edwards does not provide sufficient direction to lead one skilled in the art directly and predictably to Applicants' claimed salt or osmotic tolerant transgenic plants, but rather raises questions that might lead to further experimental inquiry For example, is the liquid culture iso-osmotic? Is the soil saturated or dry? Does environmental regulation lead to increased or decreased tolerance, or is the expression unrelated to function? As Applicants have previously noted, function cannot be inferred from expression data alone; thousands of plant genes may be up- or down-regulated in response to environmental

stimuli, and only a small minority would confer tolerance when over- or under-expressed, respectively. As previously indicated, and recognized in the latest Office action, Swindell et al. (2007) *Heredity* 99: 143–150 recognized that "[c]andidate genes with a well-supported role in stress response pathways provide good prospects for subsequent experimental study", but "[t]he identification of temperature-related genes [i.e., regulated in response to environmental changes] through microarray analysis represents only a first step towards understanding their role in cold- and heat-stress-regulatory pathways"(page 149, left column). Feder et al. (2005) *J. Evol. Biol.* 18: 901-910 further support that "[p]ublished work to date suggests that mRNA abundance typically provides little information on protein activity and fitness and cannot substitute for detailed functional and ecological analyses of candidate genes" (Abstract). In fact, Edwards makes clear that his teaching cannot be used without the undue effort of using reverse genetics to assign functionality to his listed genes: "further research is required to understand the regulation of these factors and their role in developmental and environmental responses"(page 1021, column 1, ¶2). Again, Applicants note that *responses* are reactive, and the statement does not suggest that Edwards' listed proteins proactively confer function, let alone the claimed functions.

Furthermore, the interpretation of expression data must take into account that a plant is always changing and adapting to its environment. The *response* of the transcriptome is made in a variable background that may be unique to experimental conditions. Thus, Edwards does not provide an understanding of the effects of overexpressing the sequences taught in the citation. Applicants believe that specific knowledge of which particular polynucleotides within the entire plant genome that can be used to confer salt or osmotic stress tolerance based on expression data alone cannot be made without hindsight analysis.

Applicants note that presently amended claims 69-75 are directed to methods of producing a transgenic seedling or more mature plant that is more tolerant to salt or osmotic stress. Clearly, such methods cannot be considered inherently disclosed in a reference or combination of references that nowhere suggests or teaches the use of CCAAT-box binding transcription factors such as those in the presently claimed invention in such a method.

Edwards does not teach transgenic plants with the instantly claimed sequences, and therefore cannot provide evidence that the instantly claimed sequences function in a manner different from what Harada teaches, which, as discussed below, teaches away from that which Applicants have achieved. Edwards also does not establish that the instant sequences are Lec1-related proteins.

Applicants respectfully submit that it is not obvious to try to combine Edwards and Harada

In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Supreme Court held that whether an invention is obvious under the obvious to try standard depends on (1) whether there are a finite number of identified, predictable solutions for the problem that the invention seeks to resolve, and thus, a person of

ordinary skill in the art has good reason to pursue the known options within his or her technical grasp; and (2) whether the effort leads to the anticipated success. Given that the instantly claimed sequences *are not* Lec1-related proteins, as shown below, there is not a finite number of identified, predictable solutions made by combining Edwards and Harada for the purpose of reaching the instant claims.

The skilled artisan would be aware that the instantly claimed sequences are not LEC1-related proteins, and thus are sufficiently distant from the LEC1-related proteins that no inference can be made with regard to shared functions. See, for example, US patent 7,294,759 (US20030204870), filed June 26, 2002, which teaches that "Lec1 homologs may be further identified by using conserved sequence motifs. …Underlined amino acids are those that are conserved in Lec1 *but not found in Lec1-related proteins* (*emphasis* added). Contrarily, the G482 sequence has seven different corresponding amino acids, including *all five* of the corresponding residues underlined above that are "not found in Lec1-related proteins".

7,294,759: REQDxxMPxANVxRIMRxxLPxxAKISDDAKExIQECVSExISFxTxEANxRCxxxxRKTxxxE"

G482: REQDxxLPXANVxRIMKxxLPxxAKISKDAKExMQECVSExISFxTXEASXKCxxxxRKTxxxD

Applicants also recognized differences between the above two sequences on page 29, where they describe the B domain of the non-LEC1-like clade, teaching the underlined aspartic acid in the first sequence corresponds to a lysine, the underlined asparagine of the first sequence corresponds to a serine or alanine, and the underlined arginine in the first sequence corresponds to a lysine or glutamic acid residue.

Ser/Gly-Arg-Ile/Leu-Met-Lys-$(Xaa)_2$-Lys/Ile/Val-Pro-Xaa-Asn-Ala/Gly-Lys-Ile/Val-Ser/Ala/Gly-Lys-Asp/Glu-Ala/Ser-Lys-Glu/Asp/Gln-Thr/Ile-Xaa-Gln-Glu-Cys-Val/Ala-Ser/Thr-Glu-Phe-Ile-Ser-Phe-Ile/Val/His-Thr/Ser-[Pro]-Gly/Ser/Cys-Glu-Ala/Leu-Ser/Ala-Asp/Glu/Gly-Lys/Glu-Cys-Gln/His-Arg/Lys-Glu-Lys/Asn-Arg-Lys-Thr-Ile/Val-Asn-Gly-Asp/Glu-Asp-Leu/Ile-Xaa-Trp/Phe-Ala-Met/Ile/Leu-Xaa-Thr/Asn-Leu-Gly-Phe/Leu-Glu/Asp-Xaa-Tyr-$(Xaa)_2$-Pro/Gln/Ala-Leu/Val-Lys/Gly (emphasis added)

Thus, LEC1 and the sequences in the instant claim are not orthologous.

A published sequence does not make an entire gene/protein family obvious

It is art-recognized that orthologs, which are grouped into clades, are descended from a common ancestor and generally have the same function. By being in different clades, the skilled artisan would not expect LEC1 and the sequences of the instant claims to have evolutionarily conserved functions. This is evidenced by Harada's teaching: Harada's LEC1 overexpression represses the germination process or produces plants with reduced root extension. Therefore, the combination of Edwards and Harada does not lead to seedling or older plants with increased salt or osmotic stress tolerance. It is only through Applicants' reasoned identification of functional sequences that one would know to use the claimed non-LEC1 CCAAT-box transcription factors to produce transgenic seedling or older plants with salt or osmotic stress tolerance.

The extension of the Office's reasoning is that, by combining knowledge of how to make a transgenic plant with the publication of any sequence within a gene/protein family, even non-orthologous sequences, thereafter all future claims directed to any plant transformed with any member of that family would be non-inventive. And since there are only 41 families listed in the "Arabidopsis transcription factor database" (currently at arabidopsis.med.ohio-state.edu/AtTFDB/), one would reasonably question why there are so many more than 41 US patents issued for transgenic plants that overexpress transcription factors, or why such US patents continue to issue. It is true that very close homology may make one sequence obvious in view of another, but the line of inventiveness should not be extended to the edges of an entire diverse gene/protein family. Similar functions cannot, and should not, be assumed for sequences that are in the same family but are not orthologous, and particularly for the present case as Harada confirms the distinct functions of the Lec1-related proteins and the instantly claimed sequences.

In view of the amendments to the claims and the arguments presented above, Applicants respectfully request that the rejection under 35 U.S.C. §103(b) be withdrawn.

Items 4-5. Provisional obviousness type double patenting

Applicants note that the MPEP indicates that: "The public should . . . be able to act on the assumption that upon the expiration of the patent it will be free to use not only the invention claimed in the patent but also modifications or variants which *would have been obvious* to those of ordinary skill in the art *at the time the invention was made*, taking into account the skill in the art and prior art other than the invention claimed in the issued patent" (*emphasis* added). The present application, being the earlier filed application with the earlier priority date, would not have been obvious to one of ordinary skill in light of U.S. patent application 11/069,255, since the latter did not yet exist at the time the present invention was made.

The MPEP also indicates that: "If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer." (MPEP 804(I)(B)(1)).

In light of the present amendments and arguments, Applicants believe that all other rejections may be presently overcome, and thus respectfully request that this ground of rejection be held in abeyance until patentable subject matter is defined for the present application.

CONCLUSION

Applicants believe that no additional fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Mendel Biotechnology, Inc. Deposit Account No. **50-1025.**

Respectfully submitted,
MENDEL BIOTECHNOLOGY, INC.

Date: April 15, 2010

/Jeffrey M. Libby, Reg. #48251/
Jeffrey M. Libby, Ph.D.
Reg. No. 48,251

3935 Point Eden Way
Hayward, California 94545
Phone: (510) 259-6138
Fax: (510) 264-0254

JML/jml
File: MBI-0022CIP_R3OA.doc

Attachments:
Page from 09/713,994 Appendix A: "Physiology of Overexpressor G482, Family CAAT "
Page from 09/713,994 Appendix A: "Summary of Overexpressor G482, Family CAAT"